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#13 JRP 2/22/96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Examiner: Henley III, R.

Filing Date: 11/07/94 Group Art Unit: 1205

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, on January 24, 1996

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: January 24, 1996

REQUEST FOR EXTENSION OF TIME
37 CFR §1.136(a)

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Applicant hereby requests an extension of one (1) month for filing a Response to an Office Action dated September 25, 1995. The Commissioner is hereby authorized to charge any additional fees or credit any overpayment to Deposit Account No. 08-1935.

Respectfully submitted,

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Dated: January 24, 1996

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Docket No.: 0701.027C

#14
JRP
2/22/96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

APPLICANT'S INTERVIEW SUMMARY

This is a summary of an interview held November 16, 1995, with Examiner Henley in the above case. Those present at the interview were (1) Examiner Raymond Henley III, (2) John McCullough, Senior Director of Pharmacology of Sepracor, (3) Douglas Reedich, Chief Patent Counsel of Sepracor, and (4) Philip Hansen, agent of record for the applicant.

To open the interview, Mr. Hansen sketched the history of the present case, which is a divisional of application serial number 07/896,725, now US patent 5,362,755. In the parent case the same references (Muittari, Brittain, Hawkins and Hartley) were cited against the claims, and applicants made a showing which Examiner Henley felt supported the unobviousness of the method for treating with R-albuterol as chronic medication, but did not support claims to acute medication. Applicants amended the claims in the parent case to encompass only chronic administration and the case was allowed. In the meantime, applicants have carried out additional studies that they believe fully support the remainder of the original invention, acute administration, claims to which are now pending in this application.

Dr. McCullough then discussed the June 7, 1995, Declaration of Dean A. Handley, which is of record in the case. He also discussed a new study, just completed, the

results of which will be provided in a declaration that will accompany the response to the outstanding Office Action. The studies of Dr Handley had showed three things: (1) R-albuterol is the eutomer for bronchodilation in humans; (2) S-albuterol potentiates the response to spasmogen in humans 3 hours after acute administration; and (3) all three (R- S- and R,S-albuterol) are tremorigenic. The new study, investigating intracellular calcium levels, confirms the previously submitted results concerning enhancement of response to spasmogen caused by acute administration of S-albuterol. Intracellular calcium levels are known to control contractility in smooth muscle cells. Dr. McCullough found in this study that basal Ca^{2+} levels in bovine airway smooth muscle cells were affected by acute exposure of the cells to the isomers of albuterol. Cell exposure to R-albuterol decreased basal Ca^{2+} levels. Such decreases in basal Ca^{2+} are associated with relaxation of bronchial smooth muscle. Cell exposure to S-albuterol, on the other hand, increased basal Ca^{2+} levels, and such increases are associated with contraction of bronchial smooth muscle. Indeed, in about 25% of the cells exposed to high concentrations of S-albuterol ($\geq 10^{-4}$ M) spontaneous calcium oscillations accompanied by spontaneous cell shortening was observed. No such oscillations or contractions were observed in cells exposed to R-albuterol.

Dr. McCullough explained that when cells are exposed to a spasmogen such as carbachol, two phases of increased Ca^{2+} are observed: an initial phase involving a large transient increase, and a second phase involving a sustained but lesser increase. The study showed that cell exposure to R-albuterol reduced both phases. Cell exposure to S-albuterol, on the other hand, enhanced both phases. This enhancement of

intracellular calcium represents a mechanism for bronchial hyperreactivity following acute administration of S-albuterol.

There was considerable discussion as to whether the results of the studies are adequate to overcome the rejection of record. Examiner Henley indicated that he needed to be convinced that the results were truly unexpected. Dr. McCullough noted that there is nothing in the literature to suggest adverse effects arising out of the S-enantiomer. On the contrary, one skilled in the art would have believed that the effects of albuterol, adverse and beneficial alike, reside with the R-enantiomer. No significant advantages would be expected to arise out of the use of R-albuterol compared to the racemate. Applicants' studies, however, establish that use of R-albuterol provides advantages (i.e., avoidance of hyperreactivity and reduction of tremorgenicity). One reason that these advantages are significant, Dr. McCullough explained, is because the serum half life of S-albuterol in humans is longer than that of R-albuterol. Thus, when racemic albuterol is administered, the spasmogenic and tremorgenic effects of the S-enantiomer persist long after the beneficial bronchodilatory effects of the R-enantiomer have faded. On the other hand, when R-albuterol is administered, the persistent adverse effects will be reduced (in the case of tremor) or avoided (in the case of hyperreactivity).

Examiner Henley also indicated that he needed to be convinced that *In re Adamson* is not controlling. It was pointed out that a case of *prima facie* obviousness can be overcome if it is demonstrated that the claimed invention possesses sufficient unexpected properties not actually possessed by the closest prior art. *Adamson* does not purport

to change the law in this regard. Messrs. Hansen, Reedich and McCullough agreed to prepare a response that explains what one skilled in the art would expect based on the prior art, makes clear that Applicants' results are indeed unexpected, and addresses *Adamson*.

Mr. Hansen thanked Examiner Henley for his time and the interview concluded.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Dated: January 24, 1996

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#15 2/22/96

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, January 24, 1996.

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: January 24, 1996

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE UNDER 37 C.F.R 1.116

Dear Sir:

This is in response to the Official Action of September 25, 1995. In light of a Petition for one-month extension and fee therefor, enclosed herewith, the period for response expires January 25, 1996; this response is therefore timely filed.

REMARKS

In the Office Action of September 25, 1995, the rejection of all of the claims over Muittari et al. (CK) in view of Brittain et al. (CB), Hawkins et al. (CD) and Hartley et al. (CC) was maintained and made final.

In an interview graciously granted by the examiner on November 16, 1995, (Applicants' Interview Summary Enclosed), applicants' representative agreed to submit the Declaration of Dr. John R. McCullough (submitted herewith) describing a new study investigating intracellular calcium levels. Applicants' representative also agreed to submit a response that details what one skilled in the art would expected based on the prior art, makes clear that applicants' results are indeed unexpected, and addresses *In re Adamson*, 125 USPQ 233 (CCPA 1960).

To begin, applicants dispute the assertion of *prima facie* obviousness for reasons already of record. However, even if the assertion of *prima facie* obviousness were to be deemed to be correct, the pending claims are patentable for the reasons that follow.

As for *In re Adamson*, *Adamson* sought to patent the levo (-) isomer of a known racemic spasmolytic agent. In support of patentability, data were presented showing that the levo (-) isomer was about twice as potent as the racemate and slightly less toxic than the racemate and the dextro (+) isomer. As regards the potency data, the CCPA noted that "appellants have...ascertained no more than what would be expected by one skilled in the art". Thus, patentability for *Adamson* was not allowed to reside in the discovery that one enantiomer of the racemic compound is more potent than the other. Concerning the toxicity data, the CCPA noted that they were "particularly expected". The CCPA considered the totality of the record and held that, because *Adamson* had presented nothing unexpected, the claimed invention was obvious.

The Examiner noted at the interview of November 16, 1995, that the facts in *Adamson* and in this application show the toxicity of the racemate to lie between that of the isomers. While applicants do not dispute this, it is critical that the Examiner recognize that *Adamson* does not turn on the toxicity data alone. Rather it was decided after consideration of the claims, the prior art, and the other evidence of record. It does not hold that patentability cannot lie when toxicity of the racemate is shown to lie between that of the isomers. Rather, it stands for the established proposition that patentability cannot lie when nothing unexpected is offered in rebuttal of *prima facie* obviousness.

Clearly, the very limited factual similarity between *Adamson* and this application cannot render *Adamson* controlling. It is improper to dissect the case into its factual parts and use one part to establish a *per se* rule of obviousness governing patent applications (such as this one) that fit certain facts. Moreover, even if *Adamson* was particularly relevant, it could not be used as a substitute for an analysis of patentability under 35 USC 103. The Federal Circuit has recently specifically stated that "the use of *per se* rules...flouts section 103 and the fundamental case law applying it", and that "reliance on *per se* rules of obviousness is legally incorrect and must cease" *In re Ochiai*, 37 USPQ 2d 1127, 1133 (Fed. Cir. 1995). The Examiner must consider the totality of the record, including the claims, the prior art, and the other evidence of record, in determining patentability.

By asserting that the claimed invention is *prima facie* obvious, the Patent Office is merely asserting that one

skilled in the art would have been motivated to carry out the claimed invention with a reasonable expectation of successfully achieving results comparable to those of the closest prior art. In order to rebut the assertion of *prima facie* obviousness, applicants are entitled to submit evidence of unexpected properties not actually possessed by the closest prior art. This evidence must be considered, as part of the totality of the record, in determining patentability.

What would have been expected (and unexpected) by one of ordinary skill in the art must first be determined. For this we turn to the Brittain, Hartley, Hawkins, and Buckner references. These references indicate that S-albuterol is essentially inactive at bronchial β_2 receptors at 100 times the effective dose of R-albuterol. There is nothing to indicate that any effects, adverse or beneficial, would be associated with S-albuterol. Rather, the prior art leads one of ordinary skill in the art to conclude that all of the effects of racemic albuterol, adverse and beneficial, would be possessed by the R-enantiomer. This being the case, one of ordinary skill in the art would expect the claimed method involving R-albuterol to exhibit properties substantially the same as those of the prior art method involving racemic albuterol. Substantial advantages in use of R-albuterol, on the other hand, would be unexpected.

The several declarations of record show that: (i) R-albuterol is the eutomer for bronchodilation in humans; (ii) S-albuterol increases response to spasmogen in humans after acute administration, that is, S-albuterol harms lung function by inducing bronchial hyperreactivity upon acute administration, while R-albuterol does not; (iii) all three

(R-, S-, and racemic albuterol) are tremorigenic, and (iv) enhancement of intracellular calcium represents a possible mechanism for bronchial hyperreactivity following acute administration of S-albuterol.

That R-albuterol is the eutomer is consistent with the prior art; it is not unexpected. As for parts (ii), (iii) and (iv), these very clearly demonstrate that S-albuterol is responsible for adverse effects. However, as discussed above the known adverse effects of the racemate were thought to reside in the R-enantiomer. There is nothing in the prior art to suggest that adverse effects reside in the S-enantiomer and could be avoided by use of R-albuterol, substantially free of the S-enantiomer. It is notable that the serum half life of S-albuterol in humans is longer than that of R-albuterol. Thus when racemic albuterol is administered, the spasmogenic and tremorigenic effects of the S-enantiomer persist long after the beneficial bronchodilatory effects of the R-enantiomer have faded. Reduction or avoidance of the persistent adverse effects by administering R-albuterol, substantially free of the S-enantiomer, may allow a significant improvement in acute asthma therapy.

Applicants' showing establishes that the claimed invention possesses a significant beneficial property not actually possessed by the closest prior art. Moreover, applicants have established that this property was entirely unexpected at the time the invention was made. This clearly distinguishes this application from *In re Adamson*, and more importantly is precisely what is required in order to rebut a case of *prima facie* obviousness. Accordingly, the claimed

invention has been shown to be patentable even assuming arguendo that it is *prima facie* obvious.

In view of the comments above and the accompanying declaration, applicants respectfully request reconsideration of the rejection and allowance of the pending claims.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Registration No. 32,700

Dated: January 24, 1996

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#16

RECEIVED FEB 16 AM 10:32 GROUP 120

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

DECLARATION UNDER 37 C.F.R. §1.132

I, John R. McCullough, declare that:

1. I reside at 6 Davidson Road, Worcester, Massachusetts, 01605;

2. I earned a B.A. in English with a minor in chemistry from the City University of New York in 1970, and a Ph.D. degree in Pharmacology from the State University of New York Downstate Medical Center in 1980. My primary area of research, both during my Ph.D. studies and subsequently over the ensuing fourteen years has been in cellular electrophysiology and pharmacology. I am presently Senior Director of Pharmacology at Sepracor Inc., Marlborough, Massachusetts. Prior to my employment at Sepracor, I had appointments as (sequentially) Guest Professor at the Laboratorium voor Fysiologie, Katholieke Universiteit Leuven, Leuven, Belgium; Research Associate at Northwestern University Medical Center, Chicago, Illinois; Guest Scientist at the Max Planck Institute for Biophysical Chemistry, Göttingen, Germany; Senior Scientist at CIBA-Geigy Corp., Pharmaceuticals Division, Summit, New Jersey; and Senior Research Investigator at the Bristol-Myers Squibb Institute for Medical Research, Princeton, New Jersey; I have also been an Adjunct Assistant Professor of Physiology and Biophysics at New York University Medical Center in New York, New York;

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January 22, 1996

3. I am a member of the American Association for the Advancement of Science, the Biophysical Society, the American Society for Pharmacology and Experimental Therapeutics and the Society for Neuroscience. I am a member of the editorial board of the Journal of Pharmacology and Experimental Therapeutics;

4. I am the author of 84 scientific publications in the area of pharmacology and electrophysiology and an inventor in one U.S. patent.

5. I have reviewed and do understand the contents of the above-identified application, which is directed to methods employing pure R-(-)-albuterol for the treatment of acute asthma and bronchoconstriction whereby the side effects associated with racemic albuterol are reduced. I have reviewed the Office Action in the present case, serial number 08/335,480, dated September 25, 1995, as well as the references cited therein, particularly the articles by Muittari et al., Brittain et al., Hawkins et al. and Hartley et al. I have also reviewed the Declaration Under 37 CFR §1.132 of Dean A. Handley that accompanied applicants' response of June 9, 1995.

In support of the nonobviousness of the method claimed in the above application, I present herewith experimental details and data from tests performed under my direct supervision.

BACKGROUND

In smooth muscle cells, intracellular calcium levels control contractility. Increased Ca^{2+} results in contraction, while

decreases in Ca^{2+} are associated with relaxation. Thus, any observed increase in Ca^{2+} induced by a test substance reflects an enhanced predisposition to contraction (hyperreactivity).

The effects of S- and R-Albuterol on intracellular calcium were measured in individual cells from bovine trachea loaded with fura 2 according to the method of Yamaguchi et al [Am. J. Physiol. 268, C771-C779 (1995)]. The concentration of Ca^{2+} in a single cell was determined from the ratio of fluorescence emissions resulting from excitation by alternating pulses of 337 and 380 nm light. Individual cells were maintained at 37° C on a heated stage of a Nikon inverted microscope. The microscope was used to image the cells, expose cells to ultraviolet light, and to capture the resulting fluorescence emissions. All drugs were dissolved in physiological salt solution containing 2.5 mM Ca^{2+}. Under these conditions, resting basal levels of Ca^{2+} in the isolated smooth muscle cells average 100-200 nM.

MATERIALS AND METHODS

Single-cell preparation. Tracheal smooth muscle cells were dispersed from strips (0.5 x 5 mm) of bovine trachealis muscle weighing 0.2 g total. The enzyme dispersal was done in 2.5 mL of nominally calcium-free physiological salt solution (PSS) containing collagenase (4 mg, Boehringer-Mannheim) and elastase (3 mg, Boehringer-Mannheim) for 15-25 minutes, yielding cells with consistent levels of basal $[Ca^{2+}]$. The dispersed cells were recovered in low Ca^{2+} (0.1 mM) PSS, loaded with either 0.5 or 10μM fura 2 acetoxymethyl ester (AM) for 30 min at 30-32° C, and then introduced into a heated superfusion chamber (volume = 150

μL) that had a bottom cover glass. After adherence of the cells to the glass, PSS containing normal Ca^{2+} (2.3 mM, 37° C) superfused the chamber.

Fluorescent measurement. Cells loaded with fura 2-AM were excited with computer-controlled 337- and 380-nm ultraviolet light generated by a nitrogen laser and a nitrogen laser-pumped dye laser, respectively (Laser Science, Newton, MA). Each laser alternately fired short laser pulses (3 ns) at 30 Hz. These alternating pulses of light were guided by a bifurcated quartz fiber to the epiport of the microscope, where the light intensity was reduced by 90-95% with a neutral density fiber and then focused on cells through a Nikon x 40 objective lens. The fluorescent signals emitted by cells were passed through the objective to a 455-nm dichroic mirror and 475-nm barrier filter (Omega Optics, Brattleborough, VT) and captured by a Philips-based frame transfer charge coupled device (CCD) camera made by CCTV (New York, NY) or philips Components (Slatersville, RI). The analog video signals from the camera were digitized and stored in a stand-alone imaging device (Recognition Technology, Westborough, MA). With the vertical blanking signals of the CCD camera serving as a master clock, digital outputs from the device were fed into the computer through the digital input-output board.

To measure the concentration of Ca^{2+}, background levels of light were subtracted before data acquisition, and then an area (up to 11 x 11 pixels) away from the nucleus was selected over each cell. The gray levels of fluorescence emissions stimulated by alternating pulses of 337- and 380-nm light were recorded, and

their ratios were plotted in real time for a period of 9 min. Intracellular [Ca^{2+}]i was calculated using an equilibrium dissociation constant of 386 nM, a value previously determined in bovine airway smooth muscle cells to represent Ca^{2+} binding to fura 2 in situ.

RESULTS

Acute exposure of the airway smooth muscle cells to the enantiomers of albuterol had opposite effects on basal Ca^{2+} levels. R-albuterol decreased basal levels of Ca^{2+} and S-albuterol increased them. As shown in the attached Figures 1 and 2, these effects were concentration dependent. The threshold for decrease in Ca^{2+} by R-albuterol was 5×10^{-8} M while the threshold for S-albuterol-induced increase in Ca^{2+} was 10^{-11} M. Increased Ca^{2+} results in contraction, while decreases in Ca^{2+} are associated with relaxation. Thus, the increase in Ca^{2+} induced by S-albuterol would predispose cells to contract, and in approximately 25% of the cells exposed to high concentrations of S-albuterol ($\geq 10^{-5}$ M) spontaneous calcium oscillations accompanied by spontaneous cell-shortening were observed. No calcium oscillations or contractions were observed with R-albuterol.

When exposed to a spasmogen such as carbachol, two phases of increased Ca^{2+} are observed, an initial phase involving a large transient increase and a second phase involving a sustained but lesser increase. As demonstrated in Figure 3, R-albuterol reduced both phases of carbachol-induced calcium mobilization, while S-albuterol enhanced both phases.

CONCLUSIONS

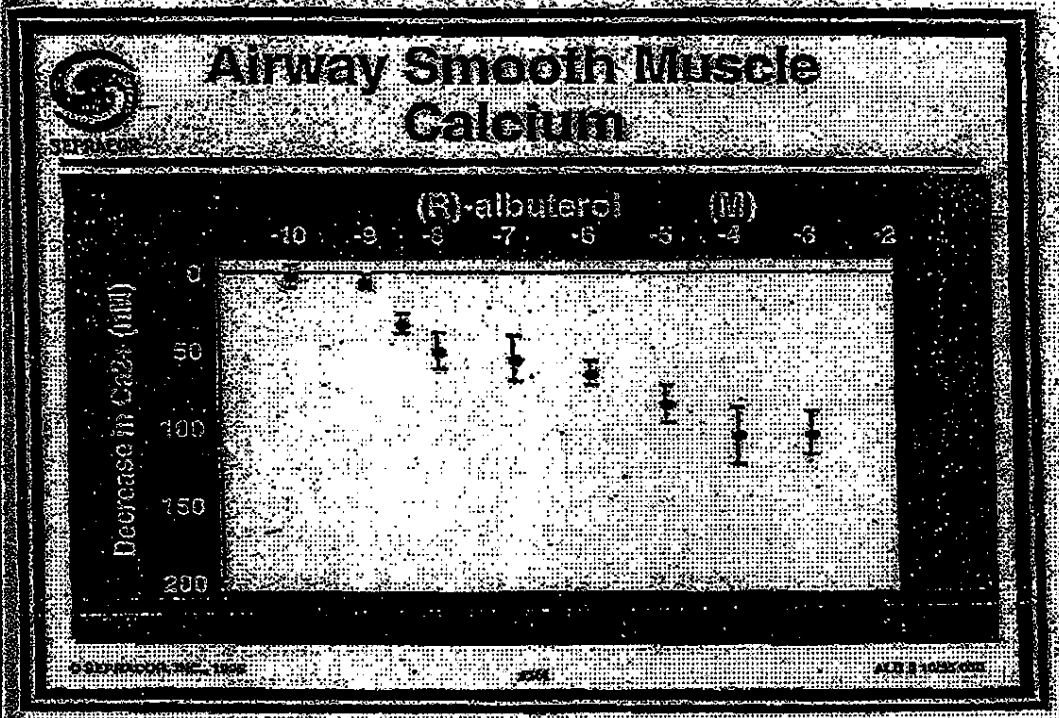
The changes in calcium handling observed in the experiments above represent a potential mechanism for bronchial hyperactivity following acute administration of S-albuterol, and further support the conclusion reached by Dr. Dean A. Handley in his Declaration Under 37 CFR 1.132 of June 7, 1995, already of record in the instant patent application. The person of skill in the art would conclude from these experiments that the use of pure R-albuterol for bronchodilation would avoid airway hyperreactivity associated with acute administration of racemic albuterol.

6. I further declare that all statements of the foregoing declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

Signed by me this 22nd day of January, 1996.

John R. McCullough

FIGURE 1


Airway Smooth Muscle Calcium
(R)-albuterol (M)
-10 -9 -8 -7 -6 -5 -4 -3 -2
Decrease in Ca2+ (nM)
0
50
100
150
200